CHRONIC TOXICITY SUMMARY

HEXAVALENT CHROMIUM (SOLUBLE COMPOUNDS)

Molecular Formula	*Molecular Weight*	*Synonyms*	*CAS Registry Number*
CrO_3	99.99 g/mol	Chromic trioxide, chromium oxide, chromium trioxide, chromium (VI) oxide. (In acid aqueous solutions, exists as H_2CrO_4 – "chromic acid")	1333-82-0
K_2CrO_4	194.20 g/mol	Potassium chromate, dipotassium chromate, potassium (VI) chromate, dipotassium monochromate, chromate of potash	7789-00-6
Li_2CrO_4	129.87 g/mol	Lithium chromate, chromium lithium oxide, chromic acid dilithium salt, lithium chromate (VI)	14307-35-8
Na_2CrO_4	161.97 g/mol	Sodium chromate, chromic acid disodium salt, chromium disodium oxide, sodium chromate (VI), chromate of soda	7775-11-3
$K_2Cr_2O_7$	294.20 g/mol	Potassium dichromate, dichromic acid dipotassium salt, bichromate of potash	7778-50-9
$Na_2Cr_2O_7$	261.96 g/mol	Sodium dichromate, bichromate of sodium, dichromic acid disodium salt, chromium sodium oxide	10588-01-9

I. Chronic Toxicity Summary

A. Soluble Hexavalent Chromium Compounds (except chromic trioxide)

Inhalation reference exposure level	**0.2 µg Cr(VI)/m^3**
Critical effect(s)	Bronchoalveolar hyperplasia in lungs of rats
Hazard index target(s)	Respiratory system
Oral reference exposure level	**0.02 mg Cr(VI)/kg/day**
Critical effect(s)	Red blood cell effects (decreased mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH)) in mice
Hazard index target(s)	Hematopoietic system

B. Chromic Trioxide (as chromic acid mist)

Inhalation reference exposure level	**0.002 µg Cr(VI)/m^3**
Critical effect(s)	Respiratory effects (nasal atrophy, nasal mucosal ulcerations, nasal septal perforations, transient pulmonary function changes) in human occupational study
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 2000; CRC, 1994)

Description	CrO_3: dark red or brown crystals, flakes, or powder, exists as chromic acid (H_2CrO_4) in solution; K_2CrO_4, Na_2CrO_4: yellow crystals; $K_2Cr_2O_7$, $Na_2Cr_2O_7$: orange-red crystals; Li_2CrO_4: yellow crystalline powder
Molecular formula	See above
Molecular weight	See above
Density	CrO_3: 2.70 g/cm^3 @ 25°C
Boiling point	CrO_3: decomposes (temperature not available); $K_2Cr_2O_7$: 500 °C with decomposition; $Na_2Cr_2O_7$: 400 °C
Melting point	CrO_3: 197 °C; K_2CrO_4: 975 °C; Na_2CrO_4: 792 °C; $K_2Cr_2O_7$: 398 °C; $Na_2Cr_2O_7$: 356.7 °C
Vapor pressure	Not applicable
Solubility	CrO_3: soluble in water, ethyl alcohol, ethyl ether, sulfuric and nitric acid; K_2CrO_4, $K_2Cr_2O_7$, $Na_2Cr_2O_7$: soluble in water, insoluble in ethyl alcohol; Na_2CrO_4: soluble in water, slightly soluble in ethyl alcohol; Li_2CrO_4: soluble in water and ethyl alcohol
Conversion factor	Not applicable for particulates and mists

III. Major Uses or Sources

Hexavalent chromium (Cr(VI)) is considerably more toxic than trivalent chromium (Cr(III)), the form most commonly found naturally (ATSDR, 1993). Cr(VI) is generally produced by industrial processes. While more information is available on the toxicity of soluble Cr(VI) compounds, information on poorly soluble Cr(VI) compounds has been included where

applicable. In California, the major emission source of Cr(VI) results from the chrome plating industry (CARB, 1997). Chromic acid, used to electroplate metal parts, is the most common Cr(VI) compound produced in the U.S. (ATSDR, 1998). Chromic acid is also registered as a fungicide and pesticide in California for use in wood and lumber protection treatments (CDPR, 1998). Chromic acid solutions used for this purpose in the most recent year of reporting (1998) was 71,109 lbs. Minute emissions of Cr(VI) may result from lead chromate in paint used for road striping and from coatings in the aerospace and auto refinishing industries, although uses of Cr(IV)-containing coatings by these industries in California are decreasing (CARB, 1997 and 1988). Use of Cr(VI) as a corrosion inhibitor in cooling tower water is prohibited in California, and recently, in the remainder of the U.S. as well. Fuel combustion releases trace amounts of chromium (CARB, 1988). Most, if not all, of this emitted chromium is in the Cr(III) state. In the chromium ferroalloy industry, sodium chromate and dichromate can be produced from imported chromite (Cr(III)) ore. However, no such facilities in California have reported production or emission of these Cr(VI) compounds.

Primary routes of potential human exposure to chromium compounds are inhalation, ingestion, and dermal contact. Exposure to chromic acid is most often in the form of a mist; exposure to other soluble forms of Cr(VI) is as components of aerosols or particulate matter. The physical, chemical, and potency differences between Cr(VI) dusts and chromic acid mists necessitated the development of separate RELs for each. Environmental exposures would most likely occur through exposure to Cr(VI) dusts (U.S. EPA, 1998). Cr(VI) may persist in water as water-soluble complex anions. However, any Cr(VI) settling in the soil or water is expected to be eventually reduced to Cr(III) by organic matter. The South Coast Air Quality Management District (SCAQMD, 2000) detected ambient levels of hexavalent chromium ranging from 0.0001 to 0.0003 $\mu g/m^3$ at 10 stationary monitors placed throughout the South Coast Air Basin. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 2311 pounds of hexavalent chromium (CARB, 2000).

IV. Effects of Human Exposure

Cr(VI) forms oxyanions at physiological pH (CrO_4^{-2}), which are quite similar to sulfate (SO_4^{-2}) and phosphate (HPO_4^{-3}) anions. Therefore, it is able to penetrate virtually every cell in the body because all cells transport sulfate and phosphate (Costa, 1997). Harmful effects are speculated to be related to the reduction of Cr(VI) to Cr(III) intracellularly when it crosses the cell membrane and forms complexes with intracellular macromolecules. Thus, Cr(VI) compounds have the potential to injure numerous organ systems. Toxicity following chronic Cr(VI) exposure has been reported in the respiratory tract, gastrointestinal system, eyes and conjunctiva, kidney, and hematopoietic system. Cr(VI) is corrosive and exposure to chromic acid mists may cause chronic skin ulcerations and upper respiratory lesions (U.S. EPA, 1998). In addition, allergic skin and respiratory reactions can occur with no relation to dose.

Nasal tissue damage has been frequently observed in chromium plating workers exposed chronically to chromic acid mists (Bloomfield and Blum, 1928; Vigliani and Zurlo, 1955; Kleinfeld and Rosso, 1965; Gomes, 1972; Sorahan *et al*., 1998). However, workers in the

chromate extraction and ferrochromium industry, exposed to particulates containing soluble Cr(VI) compounds, have also reported nasal lesions (Mancuso, 1951; Federal Security Agency, 1953; Machle and Gregorius, 1948; Wang *et al*., 1994; Walsh, 1953). Other less frequent mucous membrane injuries have been reported in workers exposed to chromate dust and chromic acid including sinusitis, laryngitis, conjunctivitis, and oral ulcerations (Mancuso, 1951; Federal Security Agency, 1953; Johansen *et al*., 1994). Nasal lesions include perforated septum, ulcerated septum, nasal atrophy, nosebleed, and inflamed mucosa following exposure to air chromium levels of about 0.1 to 5.6 mg/m^3. Exposure duration, when reported, ranged from 2 weeks to 25 years. However, there were problems in quantifying the effect for the above studies. The difficulties were primarily lack of adequate methods or data for determining exposure duration and/or exposure levels. The occupational studies summarized below provide the most reliable estimates of inhalation durations and concentrations resulting in chronic toxicity.

Workers exposed to $\geq$2 µg/m^3 Cr(VI) as chromic acid exhibited an increased incidence of nasal atrophy, nasal mucosal ulcerations, and nasal septal perforations as compared to controls (Lindberg and Hedenstierna, 1983). Workers exposed to less than 2 µg/m^3 (expressed as $\leq$ 1.9 µg/m^3) exhibited an increased incidence of irritated nasal mucosa and nasal atrophy compared to controls. The median exposure time of exposed workers was 2.5 years (range = 0.2-23.6 years). Frequency of throat and chest symptoms was similar to that of controls. The same study reported statistically significant decreases in forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and mean forced expiratory flow during the middle of the FVC in 1 second (FEF_{25-75}) measurements taken on a Thursday afternoon as compared to those taken on a Monday morning in nonsmoking workers exposed to 2 µg/m^3 Cr(VI) or more. Similar changes were observed in the smokers although only the difference in the FVC measured on a Thursday was statistically significant. No significant differences were observed between pulmonary function measurements of exposed and unexposed workers taken on a Monday morning (prior to a work week of exposure). Thus the authors infer that the observed pulmonary function changes are transient.

Nasal lesions were observed in 35 of 37 chrome platers exposed to a mean breathing zone concentration of 7.1 µg/m^3 (range = 1.4-49.3 µg/m^3) total chromium for an average of 2.2 years (range = 1.2 weeks-11 years) (Cohen *et al*., 1974). Actual exposure to Cr(VI) averaged 2.9 µg/m^3 (range = 0.09-9.1 µg/m^3). Workers employed more than one year had significantly greater nasal pathology than workers employed one year or less. Due to poor personal hygiene habits of the exposed workers, a 'direct contact' etiology may explain some of the nasal lesions.

Urinary levels of β_2-microglobulin in 24 chrome platers increased in dose-dependent fashion with increasing intensity of exposure to Cr(VI), indicating a nephrotoxic effect resulting from inhalation of Cr(VI) (Lindberg and Vesterberg, 1983). The 8-hr mean Cr(VI) levels ranged from 2 to 20 µg/m^3 and averaged 6 µg/m^3. Total exposure times ranged from 0.1 to 26 years and averaged 5.3 years. Most of the 24 chrome workers had irritation symptoms of the airways. As a group, the chrome platers had significantly higher levels of urinary β_2-microglobulin compared to a group of 27 referents. Comparison of 27 referents to a group of 27 ex-chrome-platers found no difference in urinary β_2-microglobulin levels, even though seven of the ex-chrome-platers had a permanent perforation of their nasal septum (indicating past exposure to high levels of Cr(VI)). There was no correlation between total exposure time and urinary β_2-microglobulin levels.

Urinary albumin levels remained unchanged in the Cr(VI)-exposed group. The results suggest that the nephrotoxic effects are reversible at the exposure levels studied.

Gastritis and duodenal ulcers, in addition to ulceration and perforation of the nasal septum, were observed in chrome platers exposed to a mean breathing zone concentration of 4 $\mu g/m^3$ chromic acid for an average of 7.5 years (Lucas and Kramkowski, 1975).

Male workers in the chromate and dichromate production industry, whose occupational exposures were 0.05-1.0 mg Cr(VI)/m^3 as chromium trioxide for a mean of 7 years, were reported to have elevated levels of low molecular weight proteins (retinol binding protein and tubular antigens) in the urine (Franchini and Mutti, 1988). The authors suggest that the presence of such proteins in the urine is an early indicator of kidney damage.

The respiratory health of workers exposed to low levels of dusts containing Cr(VI) was investigated at a stainless steel production plant (Huvinen *et al*., 1996). The data were presented as total chromium exposure and Cr(VI) exposure. A combined total of 109 exposed workers in the furnace department (median Cr(VI) exposure approximately 0.075-0.45 $\mu g/m^3$) and the steel smelting shop (average Cr(VI) exposure 0.5 $\mu g/m^3$) was compared to a control group of 95 workers that worked in the cold rolling mill. Total work exposure duration was 16.0 years (range: 8-26 years). No significant differences in lung function tests and radiological findings were observed between exposed and control workers. After controlling for age and smoking, no differences were observed for the prevalence of rhinitis, eye irritation, or respiratory symptoms between the two groups.

In a study summarized by U.S. EPA (1998), oral ulcers, diarrhea, stomach ache, indigestion, leukocytosis and vomiting were reported among a group of 155 Chinese villagers exposed to contaminated well-water containing 20 mg/L Cr(VI) in 1965 (Zhang and XiLin, 1987). However, precise exposure concentrations, exposure durations, and confounding factors were not provided. A follow-up study to assess cancer mortality reported that the average Cr(VI) concentration in 1965 from 170 wells of the most impacted village was only 2.6 ppm, and maximum levels did not exceed 5 ppm (Zhang and Li, 1997). Non-cancer effects were not presented and the apparent discrepancy in water levels of Cr(VI) with the earlier study was not discussed.

V. Effects of Animal Exposure

Exposure of C57BL/6 mice to 0 or 13 mg/m^3 $CaCrO_4$ dust (about 136 animals/sex/group) 5 hr/day, 5 days/wk for life resulted in emphysema-like changes of the lung, 'bronchiolarization' of the alveoli, and epithelial necrosis, marked hyperplasia, and atrophy of the bronchi in treated mice (Nettesheim *et al*., 1971). Other non-cancer histopathological findings in exposed mice included atrophy of the lymph nodes, spleen, and liver, and occasional small ulcerations of the stomach and intestinal mucosa. Cessation of body weight gain in both sexes was observed following the sixth month of exposure to the chromate dust.

Glaser *et al*. (1986) exposed 20 male Wistar rats/group to 25, 50, and 100 µg/m^3 aerosolized sodium dichromate solution and to 100 µg/m^3 of a pyrolyzed Cr(VI)/Cr(III) (3:2) oxide dust mixture 22-23 hr/day for 18 months. Observation in filtered air continued for another 12 months thereafter. A control group consisted of 40 rats. Mortality and body weights were unaffected by treatment. Lung chromium retention at the end of the study was 10-fold greater in rats exposed to the slightly water soluble chromium oxide mixture compared to high dose rats exposed to water-soluble sodium dichromate. No clinical signs of irritation were observed in any group. No hematological effects were noted in rats exposed to sodium dichromate. Rats exposed to the chromium oxide mixture had a significantly elevated white blood cell count at the 17th and 18th month, and significantly elevated red blood cells, hematocrits, and hemoglobin levels at the 27th month. Mean serum content of total immunoglobulin was significantly reduced in this group at 6 months exposure. Significantly increased lung weights were observed in chromium oxide-exposed rats, and for livers of sodium dichromate-exposed rats at the highest dose. Pigment-loaded macrophages were found in the sodium dichromate-exposed rats in a dose dependent manner and also in the chromium oxide group. Chromium oxide-exposed rats also developed focal thickened septa, partially combined with interstitial fibrosis and accumulation of eosinophilic substance in the alveolar lumens. The authors concluded that the hematological and pulmonary effects may be due to Cr-accumulation in the lungs and to depressed lung clearance function.

Rats exposed to 200 µg/m^3 Cr(VI) as aerosolized sodium dichromate by inhalation for 22 hours per day for 42 days exhibited decreased alveolar macrophage phagocytic activity; the lung clearance of inert iron oxide was significantly reduced in exposed rats compared to controls (Glaser *et al.*, 1985). Increased alveolar macrophage activity and a significantly elevated antibody response to injected sheep red blood cells were observed in rats exposed to 25 or 50 µg/m^3 Cr(VI) for 22 hours per day for 28 days. Ninety day exposure under the same exposure protocol resulted in increased rat lung and spleen weights at 50, 100 and 200 µg/m^3, but not 25 µg/m^3 (Glaser *et al.*, 1985). Histopathology of major organs was similar among all groups. Bronchoalveolar lavage fluid contained decreased macrophage cell counts above 25 µg/m^3. Increased antibody response to injected sheep red blood cells was observed in all treatment groups, while alveolar macrophage activity was elevated at 25 and 50 µg/m^3, but was significantly reduced at 200 µg/m^3.

A later experiment exposed male rats to 0, 50, 100, 200, or 400 µg Cr/m^3 22 hours per day, 7 days per week for 90 days (Glaser *et al*., 1990). Average measured concentrations were 0, 54, 109, 204, and 403 µg Cr/m^3, respectively. Subacute respiratory dyspnea and reduction in body weight gain were observed at the two highest exposures. Mean white blood cell count increased in a dose-dependent manner among treated rats, but returned to normal 30 days following cessation of exposure. Histopathological examination revealed histiocytosis (macrophage accumulation) in all treatment groups (Table 1). Bronchoalveolar lavage fluid (BALF) contained elevated levels of albumin, lactate dehydrogenase (LDH), and total protein in all exposed groups. Statistically significant elevations in these parameters were observed mainly in the 200 and 400 µg/m^3 exposure groups. At necropsy, a statistically significant increase in lung weight (g dry wt/kg body wt) was observed in rats exposed to 100, 200, and 400 µg/m^3 as compared to controls. Lung weights were still significantly elevated in the three highest exposure groups 30 days following cessation of exposure. An analysis of the data (Malsch *et al.*, 1994) determined a

benchmark dose (95% confidence interval with dose associated with a 10% elevation in the parameter) for each of these endpoints. The analysis also examined changes in lung and spleen weight reported in Glaser *et al.* (1985). The most sensitive endpoint was LDH in BALF.

Table 1. Key bronchoalveolar lavage fluid (BALF) and histopathological findings after 90 days exposure to sodium dichromate (Glaser *et al*., 1990).

µg Cr/m^3	*Total Protein in BALF*[a] *(mg/L)*	*Albumin in BALF (mg/L)*	*LDH in BALF (U/L)*	*Broncho-alveolar Hyperplasia*	*Lung Histiocytosis*	*Right lung dry weight (g/kg BW)*
0	226±30	77±13	29±5	0/10	2/10	0.44± 0.03
50	396±79**	115±23**	34±3*	3/10	9/10	0.48±0.05
100	326±35**	86±13	31±4	2/10	10/10	0.50±0.06*
200	703±178**	117±20**	63±11**	3/10	9/10	0.55±0.04**
400	975±246**	184±59**	83±17**	7/10	10/10	0.65±0.05**

[a] All BALF parameters are mean ± SD, n = 10/group
* $p < 0.05$; ** $p < 0.001$: comparison of exposed groups vs. controls

Cohen *et al*. (1998) investigated the immunotoxicologic effects of inhaled chromium by exposing F-344 rats (10/group/exposure duration) nose-only to 0 and 360 µg/m^3 potassium chromate 5 hr/day, 5 days/week for 2 or 4 weeks. Exposed rats had greater levels of total recoverable cells, neutrophils, and monocytes in bronchopulmonary lavage compared to controls at 2 and/or 4 weeks. Pulmonary macrophages (PM) were reduced, although total PM levels remained unaffected. Four-week exposure to potassium chromate also resulted in modulated PM-inducible interleukins-1 and –6, and tumor necrosis factor-α, and increased PM basal nitric oxide production and interferon-γ-primed/zymosan-stimulated reactive oxygen intermediate production.

Nasal septal perforation, hyperplastic and metaplastic changes in the larynx, trachea, and bronchus, and emphysema were observed in mice exposed two days per week for 12 months to CrO_3 mist (Adachi, 1987; Adachi *et al.*, 1986). Chromic acid concentrations were either 3.63 mg/m^3 for 30 minutes per day or 1.81 mg/m^3 for 120 minutes per day. An additional 20 mice exposed to 1.81 mg/m^3 were necropsied 6 months after the last exposure. Lesions of the nasal septum, trachea, and lungs were still evident in some mice.

The investigators of the toxicity studies summarized below administered soluble Cr(VI) compounds to experimental animals by the oral route.

Groups of eight male and eight female Sprague-Dawley rats were supplied with drinking water containing 0-11 ppm (0-11 mg/L) Cr(VI), as K_2CrO_4, for 1 year (Mackenzie *et al.*, 1958). The control group (10/sex) received distilled water. A second experiment involved three groups of 12 male and 9 female rats. One group was given 25 ppm (25 mg/L) Cr(VI); a second received 25 ppm chromium in the form of chromic chloride; and the controls received distilled water. For rats treated with 0-11 ppm (in the diet), hematological determinations (red and white blood cell counts, differential white cell counts, and hemoglobin) were performed monthly, and tissues (livers, kidneys and femurs) were examined at 6 months and 1 year. Spleens were also examined

at 1 year. The 25 ppm groups (and corresponding controls) were examined similarly, except that no animals were killed at 6 months. No significant adverse effects were seen in appearance, weight gain, or food consumption, and there were no treatment-related effects regarding hematological parameters or other tissues in any treatment group. The rats receiving 25 ppm Cr(VI) showed an approximate 20% reduction in water consumption. This dose corresponds to 2.4 mg Cr(VI)/kg/day based on actual body weight and water consumption data. An abrupt rise in tissue chromium concentrations was noted in rats treated with greater than 5 ppm. The authors stated that "apparently, tissues can accumulate considerable quantities of chromium before pathological changes result." In the 25 ppm treatment groups, tissue concentrations of chromium were approximately 9 times higher for those treated with hexavalent chromium than for the trivalent group.

Anwar *et al.* (1961) observed no significant effects in groups of female dogs (2/dose group) given 0, 0.45, 2.25, 4.5, 6.75, or 11.2 ppm Cr(VI) (as K_2CrO_4) in drinking water for 4 years. The calculated doses ranged from 0.012-0.30 mg/kg of Cr(VI).

Numerous rodent studies have been recently undertaken to investigate the reproductive and developmental effects of Cr(VI) exposure via the drinking water (Trivedi *et al*., 1989; Junaid *et al*., 1995; Murthy *et al*., 1996; Junaid *et al*., 1996a; Junaid *et al*., 1996b; Kanojia *et al*., 1996; Elbetieha and Al-Hamood, 1997; Al-Hamood *et al*., 1998; Kanojia *et al*., 1998). Exposure concentrations ranged from 250 to 5000 ppm for durations as short as five days during gestation to as long as 3 months pre-gestational exposure. In general, the longer exposures resulted in more serious reproductive and developmental effects.

Kanojia *et al*. (1998) administered 0, 250, 500, and 750 ppm potassium dichromate via drinking water to female Druckrey strain rats for 90 days prior to gestation. Based on daily water intake and final body weights, the estimated daily Cr(VI) intake was 33, 68, and 98 mg/kg-day, respectively. Ten to 15% mortality, hair loss, lethargy, aggressiveness and a significant reduction in body weight gain were observed in rats at the two highest doses. While not statistically significant, weight of the low dose rats were 32% lower than controls. All treated rats were acyclic at the end of the 90 day exposure period and an additional 15-20 days without Cr(VI) exposure were needed for the estrus cycle to start. Mating and fertility indexes decreased with increasing Cr(VI) intake. Ten rats/group were sacrificed on day 19 of gestation for fetotoxicity assessment. Significantly reduced fetal weight and increased pre- and post-implantation loss occurred at all dose levels. Gross and skeletal abnormalities in low dose fetuses included subdermal hemorrhagic patches, drooping wrists, and reduced caudal bone ossification. No gross visceral abnormalities were seen in treated groups.

Administration of potassium dichromate to rats (Kanojia *et al*., 1996) and mice (Junaid *et al*., 1996a) in drinking water at concentrations of 250, 500, and 750 ppm for 20 days prior to gestation resulted in increased post-implantation loss and decreased placental weight in both species at the lowest dose. Also at this dose level, decreased fetal weight and crown-rump length were observed in mice, and increased resorptions and decreased number of live fetuses were observed in rats. Gross and skeletal abnormalities were observed in both species beginning at the 500 ppm dose level.

Groups of Sprague-Dawley rats (NTP, 1996a) and BALB/C mice (NTP, 1996b) were administered potassium dichromate in their diet at 0, 15, 50, 100, or 400 ppm for 9 weeks (24 males and 48 females/species/group) followed by a recovery period of 8 weeks. Average Cr(VI) consumption for male/female rats were 1/1, 3/3, 6/7, and 24/28 mg/kg-day, respectively. Average Cr(VI) consumption for male/female mice were 3/5, 10/16, 21/34, and 92/137 mg/kg-day, respectively. Six males and 12 females of both species were necropsied after 3, 6, or 9 weeks of treatment or after the full recovery period. There was no treatment-related histopathology observed in kidneys, ovaries, and testes in either species. Hematological analysis revealed slight decreases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) at the highest dose in both species, which is indicative of iron deficiency. MCV and MCH were normal in these groups following the 8-week recovery period. Microscopic evaluation of the livers of mice noted cytoplasmic vacuolization of hepatocytes in treated animals beginning at 50 ppm. Also in mice, there was a slight decrease in mean body weights in the 400 ppm males (5-9%) and females (4%) and the 100 ppm females (2-4%) during the dosing periods. Feed consumption by mice was generally increased in all treated groups, particularly the 400 ppm males and females. During the recovery period, feed consumption was comparable across groups.

The NTP (1997) investigated the potential reproductive toxicity of Cr(VI) in mice using the Reproductive Assessment by Continuous Breeding protocol. Groups of 20 male and female pairs of BALB/c mice (F_0) were exposed to 0, 100, 200, and 400 ppm potassium dichromate in their diet during the continuous breeding phase (approximately 12 weeks). F_1 generation litters received the same concentration of Cr(VI) in their diet as their F_0 parents and were used for assessment of second generation reproductive toxicity at sexual maturity. There were no treatment-related changes in any of the reproductive parameters in this study. In F_1 mice, the MCV was slightly decreased in males at the two highest doses, and slightly decreased in females in all dose groups. MCH and hemoglobin were slightly reduced in high dose males and high dose females, respectively. Mean body weights of the high dose F_0 and F_1 animals were slightly decreased, and mean food consumption in the F_1 mice was elevated. Reduced mean absolute liver weights were observed in 400 ppm F_0 mice of both sexes. The mean calculated doses were 19.4, 38.6, and 85.7 mg/kg-day for F_0 males and females and 22.4, 45.5, and 104.9 mg/kg-day for F_1 males and females in the 100, 200, and 400 ppm dose groups, respectively.

In an investigation of the spermatogenic and steroidogenic effects of Cr (VI), Chowdhury and Mitra (1995) administered 0, 20, 40, and 60 mg/kg-day sodium dichromate by oral gavage to male rats for 90 days. Reduced Leydig cell population, reduced body and testicular weight, and degeneration of testicular tissue was observed at the two highest doses. Biochemical measures of spermatogenic and steroidogenic impairment, including decreased testicular DNA, RNA, protein, serum testosterone, and 3*b*-?^{5}-hydroxy steroid dehydrogenase (3*b*-?^{5}-HCH), were also reduced at the two highest doses. Only relatively small reductions in testicular protein, 3*b*-?^{5}-HCH, and serum testosterone were seen in the 20 mg/kg rats.

VI. Derivation of Chronic Reference Exposure Levels (RELs)

A. Derivation of Chronic Inhalation Reference Exposure Level for Soluble Hexavalent Chromium Compounds other than Chromic Trioxide

Study	Glaser *et al*., 1990
Study population	Male Wistar rats (30 per group)
Exposure method	Discontinuous whole-body inhalation (0, 54, 109, 204, or 403 µg Cr(VI)/m^3 as sodium dichromate aerosol)
Critical effects	Bronchoalveolar hyperplasia
LOAEL	50 µg/m^3
NOAEL	Not observed
BMC_{05}	12.50 µg/m^3
Exposure continuity	22 hr/day, 7 days/week
Exposure duration	90 days
Average exposure	11.46 µg/m^3 Cr(VI) (12.50 x 22/24)
Human equivalent concentration	24.47 µg/m^3 Cr(VI) (2.1355 [RDDR] x 11.46)
LOAEL uncertainty factor	Not needed in the BMC approach
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.2 µg/m^3 (0.0002 mg/m^3)

The study by Glaser *et al*. (1990) provides the best available inhalation data that demonstrate a dose-response relationship for various pulmonary toxicity endpoints. The BMC_{05} of 12.50 µg/m^3 was derived from quantal data for bronchoalveolar hyperplasia. The presence of bronchoalveolar hyperplasia in exposed rats is supported by other indicators of lung inflammation, including increased total protein, LDH, and albumin in BALF (see Table 1). A quantal-linear model analysis (U.S. EPA, National Center for Environmental Assessment, benchmark dose software, version 1.20) of the quantal data provided the most reasonable line fit and resulted in the lowest BMC_{05}. A BMC_{05} is considered to be similar to a NOAEL in estimating a concentration associated with a low level of risk. Lung histiocytosis (macrophage accumulation) was present in nearly all exposed animals, but this quantal data set was only suitable for a NOAEL/LOAEL approach and was not considered as direct an indicator of lung injury as bronchoalveolar hyperplasia.

Based on OEHHA methodology, a comparison REL developed using the NOAEL/LOAEL approach would yield 0.3 µg/m^3. Adjustment of the LOAEL of 50 µg/m^3 (a NOAEL was not observed) to the human equivalent concentration uses the same parameters as shown in the REL derivation above. However, a LOAEL UF of 3 is added to the existing UFs to result in a cumulative UF of 300.

The U.S. EPA (1998) RfC of 0.1 µg/m^3 is also based on data from Glaser et al. (1990), but derived a BMC_{10} (16 µg/m^3), as developed by Malsch *et al*. (1994), from continuous data of

LDH in BALF. Using a polynomial model provided by a different benchmark software package (*THC*, Clement International Corp., Ruston LA), increasing LDH concentration in BALF with increasing dose provided the lowest BMC_{10} among the various BALF endpoints. OEHHA is currently not developing BMCs for RELs based on continuous data. A BMC_{05} derived from quantal data and a BMC_{05} derived from continuous data may not have the same meaning. Conceivably, depending on the standard deviations of the data points, the BMC_{05} based on continuous data could still be above the statistically significant effect level. OEHHA believes that further evaluation of BMC's based on continuous data is needed prior to their application to RELs.

OEHHA and U.S. EPA also diverge on the assignment of the Subchronic UF. The Glaser *et al*. (1990) study indicated that chromium was still acculmulating in lung tissue at the end of 90 days. This evidence and the fact that the study did not investigate upper airway effects and other extra-pulmonary effects led U.S. EPA to assign a subchronic UF of 10 (U.S. EPA, 1998). Based on OEHHA methodology, OEHHA used a subchronic UF of 3. In support of a UF of 3, the 18-month sodium dichromate exposure study performed by Glaser *et al*. (1986), under similar exposure conditions used in the key 90-day study, did not find histopathological evidence of lung inflammation or major organ effects, or suggest severe chromium accumulation in exposed rats. However, BALF analysis was not performed in the chronic study.

For comparison with the proposed REL, the occupational study by Huvinen *et al*. (1996) established a NOAEL of 0.5 $\mu g/m^3$ for lack of pulmonary findings. However, this study is deficient for REL purposes due to the lack of a LOAEL. Unfortunately, other occupational studies suffered from lack of adequate methods or data for determining exposure duration and/or exposure levels. Use of an occupational time adjustment (10/20 m^3 inhaled/day, 5/7 days/week) and an interspecies UF of 10 for the Huvinen *et al*. (1996) study would result in an estimated REL of 0.02 $\mu g/m^3$. Average exposure duration was 16 years, so a subchronic UF of 1 was sufficient.

B. Derivation of Chronic Inhalation Reference Exposure Level for CrO_3 as Chromic Acid

Study	Lindberg and Hedenstierna, 1983
Study population	Human workers (100 exposed workers, 119 unexposed controls)
Exposure method	Occupational exposure to chromic acid mist
Critical effects	Nasal atrophy, nasal mucosal ulcerations, nasal septal perforations, transient pulmonary function changes
LOAEL	1.9 µg/m^3 established as "low exposure" group (8-hr mean $\leq$ 1.9 µg/m^3)
NOAEL	Not observed
Exposure continuity	8 hr/day (10 m^3 per 20 m^3 day), 5 days/week
Exposure duration	Mean of 2.5 years (range = 0.2 - 23.6 years)
Average exposure	0.68 µg/m^3 Cr(VI) (1.9 x 10/20 x 5/7)
Human equivalent concentration	0.68 µg/m^3 Cr(VI)
LOAEL uncertainty factor	3
Subchronic uncertainty factor	10
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.002 µg/m^3 (0.000002 mg/m^3)

The occupational exposure study of Lindberg and Hedenstierna (1983) was selected as the best available human study. A 3-fold LOAEL to NOAEL uncertainty factor (UF) was applied due to the low incidence of nasal atrophy at the LOAEL (4 out of 19) and the apparent reversibility of the lesion at this exposure level. While Lindberg and Hedenstierna (1983) did not follow-up on any of the active cases of nasal ulcerations, which occurred only in workers in the 'high exposure' group, they did note that one worker, who exhibited nasal atrophy, had no visible nasal lesions 4 months after termination of exposure.

U.S. EPA (1998) based its RfC of 0.008 µg/m^3 for exposure to chromic acid mists and dissolved Cr(VI) aerosols on the same study but established the LOAEL at 2 µg/m^3 and applied a total UF of 90 (3 each for the LOAEL to NOAEL and subchronic to chronic extrapolation, and 10 for intraspecies extrapolation). It was unclear why U.S. EPA (1998) chose UFs of 3 for LOAEL and subchronic extrapolations. It was also unclear why the total uncertainty factor was 90, rather than 100, which would be obtained by following the usual convention (that the value for uncertainty factors of "3" is actually 3.16, the square root of 10, although it is usually only quoted to 1 significant figure).

For comparison, a REL can be estimated from the Adachi *et al*. (1987) study in which mice were exposed to 1.81 mg/m^3 chromic acid mist 2 hr/day, twice a week for 12 months. Lesions were observed in treated mice throughout the respiratory tract; a NOAEL was not determined. Application of the exposure continuity adjustment (2/24 hr/day x 2/7 days/week), an RDDR of 2.26 (MMAD and sigma g roughly estimated at 5 and 3 µm, respectively), and a total UF of 300

(10 for LOAEL to NOAEL, 3 for interspecies, and 10 for intraspecies) yields a REL of 0.3 $\mu g/m^3$.

In addition to being inhaled, airborne hexavalent chromium can settle onto crops and soil and enter the body by ingestion. Thus, an oral chronic reference exposure level for soluble salts of metallic chromium(VI) is also required for assessing risks from stationary sources in the Air Toxics Hot Spots program.

C. Derivation of Chronic Oral Reference Exposure Level for Chromium VI (Based on U.S. EPA RfD)

Study	Mackenzie *et al.*, 1958
Study population	8 male and 8 female Sprague-Dawley rats
Exposure method	Drinking water
Critical effects	No adverse effects seen
LOAEL	None
NOAEL	2.4 mg/kg-day (converted from 25 mg/L of chromium as K_2CrO_4)
Exposure continuity	Continuous
Exposure duration	1 year
Average experimental exposure	2.4 mg/kg-day (0.11 ppm Cr(VI))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Oral reference exposure level	0.02 mg/kg bw-day

The oral REL (0.02 mg/kg bw-day) and U.S. EPA's oral Reference Dose (RfD) of 0.003 mg/kg-day (U.S. EPA, 1998) are based on the same study by MacKenzie *et al*. (1958). No adverse effects were reported at any dose in the study. The highest dose group (25 mg/L) was selected for derivation of the oral REL and RfD based on the reported body weight of the rat (0.35 kg) and the reported average daily drinking water consumption for the rat (0.035 L/day). Because a LOAEL was not observed in the primary study, the subchronic NTP studies provide supporting evidence to justify a REL based on MacKenzie *et al*. (1958). Cr(VI) was administered in the diet of rats for 9 weeks and a NOAEL of 6 mg/kg-day was observed for slightly depressed MCV and MCH values (NTP, 1996a). The LOAEL was 24 mg/kg-day. The NTP (1996b, 1997) also observed slightly depressed MCV and MCH values in mice, but at higher Cr(VI) concentrations. While the changes are small and may be a mild adverse effect at best, the NTP (1997) noted that decreased MCV and MCH are indicators of iron deficiency and suggested that an interaction between chromium and iron is altering erythrocyte formation. The liver effects noted in female mice in the 9 week study (NTP, 1996b) were not observed in the mouse reproductive study (NTP, 1997). Therefore, the toxicological significance of this finding is uncertain.

U.S. EPA (1998) applied UFs of 3 for subchronic, 10 for intraspecies, 10 for interspecies, and a modifying factor of 3 (to account for concerns raised by the study of Zhang and XiLin (1987)) to the NOAEL for an RfD of 0.003 mg/kg-day. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA. Because the exposure duration in the primary study was greater than 12% of the estimated lifespan of rats, OEHHA applied UF of 1 for extrapolation to chronic exposure.

U.S. EPA stated its confidence in the RfD as: Study - Low; Data Base - Low; and RfD - Low. Confidence in the chosen study is low because of the small number of animals tested, the small number of parameters measured, and the lack of toxic effect at the highest dose tested. Confidence in the database is low because the supporting studies are of equally low quality, and teratogenic and reproductive endpoints are not well studied. Low confidence in the RfD follows.

OEHHA notes that more reproduction/developmental studies have been published that support the RfD and oral REL since U.S. EPA published its findings (U.S. EPA, 1998). In general, these studies indicate that reproductive and developmental effects occur at doses greater than an order of magnitude above the NOAEL established by MacKenzie *et al*. (1958) and the NTP (1996a,b, 1997). However, the dose levels used were relatively high such that a NOAEL was typically lacking.

VII. Data Strengths and Limitations for Development of the REL

The major strength of the inhalation REL for chromic acid mist is the use of human data. The major uncertainties for this inhalation REL is the lack of controlled and quantified exposure data and the lack of a NOAEL in the key chromic acid study.

The suitably thorough analysis of lower airway effects and the development of a BMC from continuous data are strengths for the Cr(VI) dust inhalation REL. Limitations include the lack of comprehensive data on multi-organ effects, the lack of chronic studies, the lack of upper airway analysis in the key study, and the lack of quantified exposure data in humans. The animal studies by Glaser *et al*. (1990, 1986) suggest that the lower respiratory airway is a primary target for Cr(VI) dusts. However, occupational studies (Mancuso, 1951; Federal Security Agency, 1953; Machle and Gregorius, 1948; Wang *et al*., 1994; Walsh, 1953) indicate that nasal lesions result from exposure to Cr(VI) dusts and may, in fact, be the most sensitive indicator of human toxicity resulting from exposure to soluble Cr(VI) dusts. However, this finding is attenuated by the fact that dermal exposure to chromic acid and Cr(VI) dusts due to poor hygienic practices of workers may overestimate the airborne concentrations necessary to result in nasal lesions.

The major strength for the oral REL is the consistency of the doses resulting in NOAELs and/or LOAELs among the major and supporting studies. The major limitations for the oral REL, other than the ones noted above by U.S. EPA, are the lack of lifetime exposure studies in experimental animals and the lack of adequate oral human exposure data.

VIII. References

Adachi S, Yoshimura H, Katayama H, Takemoto K. 1986. [Effects of chromium compounds on the respiratory system. IV. Long term inhalation of chromic acid mist in electroplating to ICR female mice.] Sangyo Igaku (Jpn. J. Ind. Health) 28:283-287. [cited in ATSDR, 1993].

Adachi S. 1987. [Effect of chromium compounds on the respiratory system. V. Long term inhalation of chromic acid mist in electroplating by C57BL female mice and recapitulation on our experimental studies.] Sangyo Igaku (Jpn. J. Ind. Health) 29:17-33. [cited in ATSDR, 1993].

Al-Hamood MH, Elbetieha A, and Bataineh H. 1998. Sexual maturation and fertility of male and female mice exposed prenatally and postnatally to trivalent and hexavalent chromium compounds. Reprod. Fertil. Dev. 10:179-183.

ATSDR. 1993. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Chromium. Prepared by Syracuse Research Corporation under subcontract to Clement International Corporation under Contract No. 205-88-0608. Prepared for U.S. Department of Health and Human Services, Public Health Service, ATSDR.

ATSDR. 1998. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Chromium. Prepared by Sciences International under subcontract to Research Triangle Institute under Contract No. 205-93-0606. Prepared for U.S. Department of Health and Human Services, Public Health Service, ATSDR.

Anwar RA, Langham, FF, Hoppert CA, Alfredson BV, and Byerrum RU. 1961. Chronic toxicity studies. III. Chronic toxicity of cadmium and chromium in dogs. Arch. Environ. Health 3:456-460.

Bloomfield JJ, and Blum W. 1928. Health hazards in chromium plating. Public Health Rep 43:2330-2351.

CARB. 1988. California Air Resources Board. Proposed Hexavalent Chromium Control Plan. Staff Report. Date of Release: January 1988.

CARB. 1997. California Air Resources Board. Toxic Air Contaminant Identification List (Summaries). Date of release: September 1997.

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CDPR. 1998. California Department of Pesticide Regulation. Summary of Pesticide Use Report Data, 1998, Indexed by Chemical. http://www.cdpr.ca.gov/docs/pur/pur98rep/chmrpt98.pdf

Chowdhury AR, and Mitra C. 1995. Spermatogenic and steroidogenic impairment after chromium treatment in rats. Indian J. Exp. Biol. 33:480-484.

Cohen MD, Zelikoff JT, Chen L-C, and Schlesinger RB. 1998. Immunotoxicologic effects of inhaled chromium: Role of particle solubility and co-exposure to ozone. Toxicol. Appl. Pharmacol. 152:30-40.

Cohen SR, Davis DM, and Kramkowski PE. 1974. Clinical manifestations of chromic acid toxicity: Nasal lesions in electroplate workers. Cutis 13:558-568.

Costa M. 1997. Toxicity and carcinogenicity of Cr(VI) in animal models and humans. Crit. Rev. Toxicol. 27(5):431-442.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Elbetieha A, and Al-Hamood MH. 1997. Long-term exposure of male and female mice to trivalent and hexavalent chromium compounds: effect on fertility. Toxicology 116:39-47.

Federal Security Agency. 1953. Health of workers in chromate producing industry. A study. U.S. Public Health Service Publication No. 192. Washington, DC. U.S. Government Printing Office.

Franchini I, and Mutti A. 1988. Selected toxicological aspects of chromium (VI) compounds. Sci. Total Env. 71:379-387. [cited in ATSDR, 1993].

Glaser U, and Hochrainer H. 1988. Report on the subchronic inhalation toxicity of sodium dichromate in rats with attachment and cover letter dated 112089. Industrial Health Foundation Inc. Available from: EPA\OTS Doc#FYI-OTS-1289-0729; Fiche No. OD-NTIS/OTS 0000729.

Glaser U, Hochrainer D, Kloppel H, and Oldiges H. 1986. Carcinogenicity of sodium dichromate and chromium (VI/III) oxide aerosols inhaled by male Wistar rats. Toxicology 42:219-232.

Glaser U, Hochrainer D, Kloppel H, and Kuhnen H. 1985. Low level chromium (VI) inhalation effects on alveolar macrophages and immune functions in Wistar rats. Arch. Toxicol. 57:250-256.

Glaser U, Hochrainer D, Steinhoff, D. 1990. Investigation of irritating properties of inhaled Cr(VI) with possible influence on its carcinogenic action. In: Environmental Hygiene II. Seemayer NO, Hadnagy W. (eds.) Berlin/New York: Springer-Verlag.

Gomes ER. 1972. Incidence of chromium-induced lesions among electroplating workers in Brazil. Ind. Med. 41(12);21-25.

HSDB. 2000. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD. Available online through Toxicology Data Network at http://toxnet.nlm.nih.gov

Huvinen M, Uitti J, Zitting A, Roto P, Virkola K, Kuikka P, Laippala P, and Aitio A. 1996. Respiratory health of workers exposed to low levels of chromium in stainless steel production. Occup. Environ. Med. 53:741-747.

Johansen M, Overgaard E, and Toft A. 1994. Severe chronic inflammation of the mucous membranes in eyes and upper respiratory tract due to work-related exposure to hexavalent chromium. J. Laryngol. Otol. 108:591-592.

Junaid M, Murthy RC, and Saxena DK. 1995. Chromium fetotoxicity in mice during late pregnancy. Vet. Hum. Toxicol. 37(4):320-323.

Junaid M, Murthy RC, and Saxena DK. 1996a. Embryo- and fetotoxicity of chromium in pregestationally exposed mice. Bull. Environ. Contam. Toxicol. 57:327-334.

Junaid M, Murthy RC, and Saxena DK. 1996b. Embryotoxicity of orally administered chromium in mice: Exposure during the period of organogenesis. Toxicol. Lett. 84:143-148.

Kleinfeld M, and Rosso A. 1965. Ulcerations of the nasal septum due to inhalation of chromic acid mist. Ind. Med. Surg. 34:242-243.

Kanojia RK, Junaid M, and Murthy RC. 1996. Chromium induced teratogenicity in female rat. Toxicol. Lett. 89:207-213.

Kanojia RK, Junaid M, and Murthy RC. 1998. Embryo and fetotoxicity of hexavalent chromium: a long-term study. Toxicol. Lett. 95:165-172.

Lindberg E, and Hedenstierna G. 1983. Chrome plating: symptoms, findings in the upper airways, and effects on lung function. Arch. Environ. Health 38(6):367-374.

Linberg E, and Vesterberg O. 1983. Urinary excretion of proteins in chromeplaters, exchromeplaters and referents. Scand. J. Work. Environ. Health 9:505-510.

Lucas JB, and Kramkowski RS. 1975. Health hazard evaluation/ toxicity determination report H.H. 74-87-221 Industrial Platers Inc. Columbus, OH. Cincinnati, OH: National Institute for Occupational Safety and Health. NTIS #PB 249 401.

Machle W, and Gregorius F. 1948. Cancer of the respiratory system in the United States chromate-producing industry. Public Health Rep 63(35):1114-1127.

MacKenzie RD, Byerrum RU, Decker CF, Hoppert CA, and Langham RF. 1958. Chronic toxicity studies. II. Hexavalent and trivalent chromium administered in drinking water to rats. AMA Arch. Ind. Health. 18:232-234.

Malsch PA, Proctor DM, and Finley BL. 1994. Estimation of a chromium inhalation reference concentration using the benchmark dose method: A case study. Regul. Toxicol. Pharmacol. 20:58-82.

Mancuso TF. 1951. Occupational cancer and other health hazards in a chromate plant: A medical appraisal. II. Clinical and toxicologic aspects. Ind. Med. Surg. 20(9):393-407.

Murthy RC, Junaid M, and Saxena DK. 1996. Ovarian dysfunction in mice following chromium (VI) exposure. Toxicol. Lett. 89:147-154.

Nettesheim P, Hanna MG Jr., Doherty DG, Newell RF, and Hellman A. 1971. Effect of calcium chromate dust, influenza virus, and 100 R whole-body x radiation on lung tumor incidence in mice. J. Natl. Cancer Inst. 47(5):1129-1144.

NTP. 1996a. National Toxicology Program. Final report on the reproductive toxicity of potassium dichromate (hexavalent) (CAS No. 7778-50-9) administered in diet to SD rats. Research Triangle Park, NC. December 16, 1996.

NTP. 1996b. National Toxicology Program. Final report on the reproductive toxicity of potassium dichromate (hexavalent) (CAS No. 7778-50-9) administered in diet to BALB/c mice. Research Triangle Park, NC. January 10, 1997.

NTP. 1997. National Toxicology Program. Final report on the reproductive toxicity of potassium dichromate (hexavalent) (CAS No. 7778-50-9) administered in diet to BALB/c mice. Research Triangle Park, NC. February 25, 1997.

Sorahan T, Burges DCL, Hamilton L, and Harrington JM. 1998. Lung cancer mortality in nickel/chromium platers, 1946-95. Occup. Environ. Med. 55:236-242.

SCAQMD. 2000. South Coast Air Quality Management District. MATES-II. Multiple Air Toxics Exposure Study in the South Coast Air Basin. Final Report. Diamond Bar, CA: SCAQMD. March. p. 3-10.

Trivedi B, Saxena DK, Murthy RC, and Chandra SV. 1989. Embryotoxicity and fetotoxicity of orally administered hexavalent chromium in mice. Reprod. Toxicol. 3:275-278.

U.S. EPA. 1984. United States Environmental Protection Agency. Health Assessment Document for Chromium. Environmental Criteria and Assessment Office, Office of Research and Development. Research Triangle Park, NC: U.S. EPA.

U.S. EPA. 1996. Integrated Risk Information System (IRIS). Chromium (VI).

U.S. EPA. 1998. United States Environmental Protection Agency. Toxicological Review of Hexavalent Chromium. In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC.

Vigliani EC, and Zurlo N. 1955. Erfahrung der Clinica del Lavoro mit einigen maximalen Arbeitsplatzkonzentrationen (MAK) von Industriegiften. Arch. Gewerbepath. Gewerbhyg. 13:528-534. (Ger.)

Walsh EN. 1953. Chromate hazards in industry. JAMA 153(14):1305-1308.

Wang X, Qin Q, Xu X, Xu J, Wang J, Zhou J, Huang S, Zhai W, Zhou H, and Chen J. 1994. Chromium-induced early changes in renal function among ferrochromium-producing workers. Toxicology 90:93-101.

Zhang J, and XiLin L. 1987. Chromium pollution of soil and water in Jinzhou. J. Chinese Prevent. Med. 21:262-264.

Zhang J, and Li S. 1997. Cancer mortality in a Chinese population exposed to hexavalent chromium in water. J. Occup. Environ. Med. 39(4):315-319.